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Canadian Adverse Reaction Newsletter

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In this Issue

Valdecoxib (Bextra™): severe cutaneous reactions 1
Natural health products 2
Case presentations:
- Ciprofloxacin 3
- Finasteride 3

Drug Safety Information Workshop II Report 3
Human growth hormone (somatropin): Prader–Willi syndrome 4
Summary of advisories 4

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada or a Regional AR Centre free of charge

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca
Form available at:
www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf

Valdecoxib (Bextra™): severe cutaneous reactions

Valdecoxib (Bextra™), a selective inhibitor of cyclo-oxygenase 2 (COX-2), is indicated for the treatment of acute and chronic signs and symptoms of adult rheumatoid arthritis and osteoarthritis as well as for the relief of pain associated with primary dysmenorrhea.[1]

Severe cutaneous adverse reactions (ARs) associated with valdecoxib, including erythema multiforme (EM), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported internationally.[2] This resulted in the issuance of a Dear Health Care Professional Letter in Canada to coincide with the Canadian launch of valdecoxib (Bextra™).[3] The Canadian product monograph[1] contains the following important safety information:

- a warning about the risk of serious cutaneous reactions;
- a recommendation to discontinue valdecoxib therapy at the first appearance of a rash or other sign of hypersensitivity;
- a contraindication for use in patients who have had allergic-type reactions to sulfonamides;
- a contraindication for use in patients who have experienced asthma, urticaria or an allergic-type reaction after taking ASA or other NSAIDs.

Health Canada received 9 Canadian reports of suspected cutaneous ARs associated with valdecoxib from the date of marketing, Dec. 11, 2002, to Aug. 1, 2003. Five cases were labelled serious; however, none of the patients had EM, SJS or TEN. There were no reported deaths. Two of the 5 serious reports indicated a history of allergy to sulfonamides. Given the seriousness of SJS and TEN, physicians should not prescribe valdecoxib to patients with any previous allergic reactions to sulfonamides[1] and should exert caution when prescribing it to patients prone to multiple drug allergies.[4]

In a published case report, a patient with a previous allergy to an antimicrobial sulfonamide was diagnosed with TEN after treatment with valdecoxib.[5] Controversy exists regarding the potential for cross-reactivity between sulfonamide antimicrobials and other sulfonamide-containing compounds.[6] A recent study reported that cross-reactivity between antimicrobial sulfonamides and celecoxib appears to be low.[6] Another study suggests that a predisposition to allergic reactions, rather than a cross-reactivity with sulfonamide-based drugs, is possible.[4] Health Canada has received reports of serious cutaneous reactions associated with celecoxib and rofecoxib in patients with and without a history of sulfa allergy. Valdecoxib and celecoxib have similar structures: both contain a benzenesulfonamide moiety.[5] The structure of rofecoxib contains a methylsulfonyl moiety.[5]

At least 50% of patients with SJS and TEN experience a 1- to 14-day prodrome of flu-like symptoms, including fever, malaise, rhinitis, chest pain, vomiting, sore throat, cough, diarrhea, headache, myalgia and arthralgia.[7] The progression from rash to desquamation can occur within a

2008-02538/

few days, or hours, and may result in fatal complications, such as infection and renal or respiratory failure.[8,9] It has previously been shown that early discontinuation of drugs with half-lives of less than 24 hours may decrease the rate of death from TEN and SJS.[8] Because valdecoxib has a half-life of about 8 hours,[1] withdrawal of this drug when flu-like symptoms develop may decrease the risk of TEN and SJS in certain patients. Therefore, health care professionals should encourage patients taking valdecoxib to seek medical attention if any cutaneous or flu-like symptoms occur.[1]

Violetta Skalski, PhD, Health Canada

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Natural health products and adverse reactions

The Natural Health Products Regulations are in force as of January 2004[1] and will be implemented in stages over 6 years. As with other product lines, reporting of ARs to natural health products is now mandatory for industry. Also, because of their role in reporting ARs, health care professionals and consumers need to be aware of the AR reporting system for natural health products.

We chose 3 popular herbal medicines (echinacea, ginkgo biloba and St. John's wort) to illustrate some current safety concerns associated with the use of natural health products. We searched Health Canada's database of spontaneous ARs for the period Jan. 1, 1998, to June 30, 2003.

Echinacea

Echinacea species belong to the same family as ragweed and daisies (*Asteraceae*). Allergic reactions, including anaphylaxis, following the use of echinacea have been reported.[2] The Health Canada database had 23 reports of suspected ARs associated with echinacea; 4 cases were allergic reactions, 3 of which involved single-ingredient products. Symptoms ranged from rash to swelling of the tongue and lips, to anaphylactic reaction.

Ginkgo biloba

There were 21 reports of suspected ARs associated with ginkgo. Most involved platelet, bleeding and clotting disorders, which is in line with its ability to inhibit platelet activating factor. One report was of a fatal gastrointestinal hemorrhage in which the suspect products included ticlopidine and ginkgo, both taken over 2 years, along with multiple concomitant medications. There was also a report of stroke in a patient taking multiple drugs, including clopidogrel and ASA, as well as an herbal product containing ginkgo. Caution should be exercised when ginkgo is used concomitantly with anticoagulants and drugs that affect platelet aggregation (e.g., warfarin, ASA, NSAIDs,[3-5] ticlopidine and clopidogrel). Patients also need to heed medical instructions regarding pre- and postoperative use of herbal products; for example, it has been recommended that patients stop taking ginkgo at least 36 hours before surgery.[6]

St. John's wort

Because St. John's wort (*Hypericum perforatum*) is a potent inducer of cytochrome P450 (CYP)3A4, its concomitant use with CYP3A4 substrates may result in subtherapeutic levels of these drugs and may necessitate increased dosage requirements.[7,8] St. John's wort may trigger serotonin syndrome, a result of potentiated serotonin (5-HT) reuptake inhibition when St. John's wort is taken concomitantly with 5-HT reuptake inhibitors or other drugs that enhance serotonergic activity (e.g., triptans).[4,9] There were 45 reports of suspected ARs associated with St. John's wort. The most common reactions involved central and peripheral nervous system disorders and psychiatric disorders. Of the psychiatric reactions, 2 cases involved suspected serotonin syndrome as a result of an interaction with sertraline, and 1 case included symptoms suggestive of serotonin syndrome as a result of an interaction with venlafaxine. There were 2 cases in which St. John's wort was suspected of inducing mania (1 involved concomitant lithium and the other concomitant bupropion treatment).

Many natural health products contain 2 or more herbal ingredients, all of which, including nonmedicinal ingredients, would need to be considered in an AR report. Currently, for most natural health products without a Drug Identification Number, or DIN, the concentrations of herbs or active ingredients may not be provided, and specific product dosage information may not be available, which makes it difficult to determine the exact dosage the patient received. Furthermore, different species within the same genus of an herb exist, and different plant parts (root or aerial parts) containing varying concentrations of phytochemicals may be used.[10] Not all products state the species of plant or plant part on their labels, which adds to the

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challenges of reporting and assessing ARs associated with herbal medicines.

Health Canada's new regulations will facilitate reporting ARs associated with natural health products. For example, every registered product will have a unique Natural Product Number, or NPN, which will enable Health Canada to determine more easily the number and identity of ingredients contained in the product. Despite the new regulations, it will take up to 6 years before the above provisions are widely adopted by industry.

Jenna Griffiths, MSc, PhD; Scott Jordan, PhD; Karen Pilon, RN, Health Canada

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Key points for health care professionals

- Serious adverse reactions (ARs) may occur in association with natural health products (e.g., herb–drug interactions).
- Patients may not admit to using natural health products or report ARs associated with their use. Ask your patients about their use of such products and note it in their medication profile.
- Report suspected ARs to Health Canada or a Regional AR Reporting Centre toll free (tel 1-866-234-2345; fax 1-866-678-6789). Use the AR form and guidelines available on line (www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_report_e.html) or in the *Compendium of Pharmaceuticals and Specialties*.
- In your AR reports, provide detailed information about the product (e.g., exact brand name, manufacturer, ingredients listed on label) to facilitate the evaluation by Health Canada.
- Encourage patients to seek medical advice before using natural health products.
- Increase patients' awareness about their safe use.

Case Presentations

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Ciprofloxacin: suspected association with deafness and reduced hearing

Health Canada has received 4 serious case reports of deafness or decreased hearing suspected to be associated with ciprofloxacin. They involved men aged 35, 47, 65 and 67 years old. Three were receiving 1000 mg/d orally and one was receiving 800 mg intravenously. In all cases, the reactions began within 1 week after initiation of therapy. Three patients recovered, and the fourth experienced partial permanent deafness.

Finasteride: suspected association with depression

A white man in his mid-40s with no prior history of psychiatric problems was treated with finasteride for male-pattern hair loss. Clinical depression developed about 3 months after the onset of therapy. The depression was described as moderately severe but was unresponsive to treatment with various antidepressants. Treatment was maintained for 4 years. Following cessation of the finasteride therapy, the depression resolved in about 2 weeks, and the patient made a complete recovery. A published report has described 19 cases (14 males, 5 females) in whom moderate to severe depression developed during treatment with finasteride (1 mg/d orally) for androgenetic alopecia.[1]

Reference

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Communicating Drug Safety Information Workshop II: summary report available

In March 2003, Health Canada hosted the second of two invitational workshops entitled *Communicating Drug Safety Information*. This workshop was a follow-up to the first one, held Nov. 29–30, 2001.

The March workshop, whose theme was "A Shared Responsibility," brought together health care practitioners, patient and consumer advocacy groups, health professional associations and industry representatives. Participants examined the current practices for collecting and communicating drug safety information and discussed strategies to enhance their efficiency and effectiveness. The 2 summary reports highlighting the discussions are available at www.hc-sc.gc.ca/english/protection/drugs.html.

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Human growth hormone (somatropin) and use in children with Prader–Willi syndrome

The US Food and Drug Administration issued a Dear Health Care Professional Letter in association with Pfizer Inc. on May 30, 2003, regarding the long-term use of the human growth hormone Genotropin® (somatropin) in children with Prader–Willi syndrome.[1] Pfizer is aware of 7 deaths worldwide associated with one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection. The US product monograph has recently been amended to contraindicate the use of growth hormone in children with PWS who have severe obesity or severe respiratory impairment, and warnings have been added recommending that physicians evaluate these patients for upper airway restriction before prescribing growth hormone therapy.

In Canada, 7 somatropin products have a notice of compliance (Biotropin and Genotropin [not marketed in Canada], Humatrope®, Nutropin®, Protropin®, Saizen® and Serostim®). None of them is indicated for use in PWS. Although somatropins are not indicated for PWS in Canada, should a physician decide that their use is in a patient's best interest, the physician should assess the patient for severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection before prescribing this therapy.[1]

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Reference

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Summary of health professional and consumer advisories posted from Sept. 1 to Nov. 14, 2003
(advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html)

Date	Product	Subject and type
Nov 14	Stamen and Bell Magicc Bullet	Health Canada warns public not to use Stamen and Bell Magicc Bullet — consumer information
Nov 12 & 10	Ventolin® Diskus®, Serevent® Diskus®, Flovent® Diskus®	Important safety information regarding the recall of Ventolin® Diskus®/ Serevent® Diskus®/ Flovent® Diskus® — GlaxoSmithKline Inc. — consumer information and health professional communication
Nov 6	ZENAPAX®	Important new safety information regarding ZENAPAX (daclizumab) — Hoffmann–La Roche Limited — notice to hospitals
Nov 10	Nefazodone	Health Canada is overseeing the market withdrawal of the antidepressant drug nefazodone — consumer information
Oct 2	LinNefazodone	Important safety information regarding the discontinuation of sales of nefazodone in Canada — Linson Pharma — health professional communication / letter to pharmacists and wholesalers
Oct 2	Serzone-SHT$_2$®	Important safety information regarding the discontinuation of sales of nefazodone in Canada — Bristol-Myers Squibb Canada — health professional communication / letter to pharmacists and wholesalers
Sept 30	3TC®, Ziagen®, Viread™	Important safety information regarding early virologic non-response in patients with HIV infection treated with 3TC® (lamivudine), Ziagen® (abacavir) and Viread™ (tenofovir) — GlaxoSmithKline Inc. — health professional communication
Sept 15	ReFacto®	Important safety information about ReFacto® (moroctocog alfa), antihemophilic factor (recombinant) [BDDrFVIII] — Wyeth Canada — health professional communication
Sept 10	Effexor®, Effexor® XR	Important safety information regarding the use of Effexor® (venlafaxine HCl) tablets and Effexor® XR (venlafaxine HCl) capsules in children and adolescents — Wyeth Pharmaceuticals — health professional communication
Sept 4 & Aug 15	Serevent®	Important safety information regarding Serevent® (salmeterol xinafoate) in asthma and cessation of the SMART (Salmeterol Multi-center Asthma Research Trial) — GlaxoSmithKline Inc. — consumer information and health professional communication
Aug 25	Dahedi Insulin Pumps	Urgent product recall on Dahedi insulin pumps — Disetronic Medical Systems Inc. — consumer information and health professional communication
Aug 25	Panomat Infusion Pump	Urgent safety alert on your Panomat infusion pump — Disetronic Medical Systems, Inc. — consumer information and health professional communication
Aug 11	Disetronic H-TRON, H-TRONplus and D-TRONplus Insulin Pumps	Product correction and removal on Disetronic H-TRON, H-TRONplus and D-TRONplus Insulin Pumps — Disetronic Medical Systems, Inc. — consumer information and health professional communication

To receive the Newsletter and health product Advisories by email, join Health Canada's *Health_Prod_Info* mailing list. **Go to www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_e.html.**

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Suggestions?
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